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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/701,022 | 11/04/2003 | W. French Anderson | 219974 | 6505 |

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| EXAMINER | |
|---|---|
| WEHBE, ANNE MARIE SABRINA | |
| **ART UNIT** | **PAPER NUMBER** |
| 1632 | |

DATE MAILED: 04/25/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/701,022 | ANDERSON ET AL. | |
| | Examiner | Art Unit | |
| | Anne Marie S. Wehbe | 1632 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) 15-29 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 15-29 is/are rejected.

7)☒ Claim(s) 15-29 is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 11/4/04, 12/8/04.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

**DETAILED ACTION**

This is a reissue application based on U.S. Patent No. 5,399,346 issued from U.S. application no. 08/220,175. Applicant's preliminary amendment filed on 11/4/03 canceled claims 1-14, which are all of the claims in the patent, and added new claims 15-29. Claims 15-29 are currently pending in this reissue application.

Claims 15-29 are rejected under 35 U.S.C. 251 and 37 CFR 1.658 as corresponding to the count lost in Interference No. 104,712. Interference No. 104,712 was between the Junior Party, W. French Anderson, R. Michael Blaese, and Steven A. Rosenberg (5,399,346) and Senior Party, Jeffrey R. Morgan and Richard C. Mulligan (08/153,275). The judgment in Interference No. 104,712 was adverse for both parties. In Paper No. 91 of the interference proceedings, which is also paper no. 28 of application 08/220,175, and which was mailed to applicants on 6/28/02, the judgment states that, " Anderson is not entitled to a patent containing claims 1-14 of Anderson's 5,399,346 patent, which correspond to count 1" (see page 2 of the Judgment). The applicants did not file a request for reconsideration of this decision within one month after the date of the decision under 37 CFR 1.658(b), or file an appeal to the Court of Appeals for the Federal Circuit or civil action in a United States district court under 35 U.S.C. 141 or 146 respectively. The judgment of the Board of Patent Appeals and Interferences is therefore a final decision for the purpose of judicial review, see 37 CFR 1.658(a).

It is further noted according to 37 CFR 1.658(c) that this judgment settles all issues which were raised and decided in the interference or could have been properly raised and decided in the interference by motion or additional interference. See also MPEP 2358.

Since all claims present in 5,399,346 patent were deemed to correspond to the count, no additional counts having been added to the interference proceedings, the adverse judgment invalidated all claims in the 5,399,346 patent. Therefore, following the decision by the Board, U.S. Patent 5,399,346 was in effect dedicated to the public and effectively expired. A reissue application cannot be granted for an expired patent.

Claims 15-29 are further objected to under 37 CFR 1.633 on the grounds of estoppel. As noted above, the Judgment in Interference No. 104,712 determined that Anderson is not entitled to a patent containing claims 1-14 of Anderson's 5,399,346 patent, which correspond to count 1 (Judgment, page 2). The applicant explains in their declaration that they are seeking to overcome the prior art identified in the interference proceedings by amending the claims to add limitations which the applicants feel are not taught by ADA protocol or the TNF protocol. As such, patent claim 1, now canceled, has been replaced with independent claims 15 and 27. New claim 15 further limits original claim 1 to wherein the therapeutic protein expressed is cytokine other than TNF. Note however, that canceled claim 10 was limited to therapeutic proteins which are cytokines. The limitations in new dependent claims 16-22 are identical to those in canceled claims 2-7 and 12. Again, note in particular that canceled claim 12, which recites wherein the therapeutic protein expressed is an interleukin is essentially identical to new claim 22. The only real difference between the patented claims and new claim 15 is that new claim 15 seeks to

exclude the embodiment of TNF. New claim 27 further limits original claim 1 to wherein the human cells are human B-lymphocytes. Please note that this embodiment corresponds exactly to canceled claim 7. From this analysis, it is clear that the subject matter of new claims 15-29 corresponds to the lost count. The applicant further did not attempt to separate the subject matter of patent claims 7, 10 and 12 from the count. The applicant failed to file a motion under 37 CFR 1.633(c)(1) seeking to add a separate count to methods wherein the therapeutic protein is a cytokine other than TNF or wherein the human cells are B lymphocytes. Having lost the interference, Anderson et al. is therefore estopped from obtaining a patent containing claims to the methods reciting cytokines other than TNF or to human cells which are B lymphocytes. See 37 CFR 1.633 and MPEP 2363.03.

Claim 23 is rejected under 35 U.S.C. 251 as being based upon new matter added to the patent for which reissue is sought. The added material which is not supported by the prior patent is as follows: claim 23 contains the limitation that the cytokine is granulocyte-macrophage colony stimulating factor. The specification does not recite this species of cytokine. The only species listed in the specification are TNF, interleukins 1-12, and the alpha, beta, and gamma interferons (see column 5, lines 20-24).

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 15-29 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims as written are directed to two distinct methods: 1) a process for providing a human with a therapeutically effective amount of a therapeutic protein which is a cytokine other than TNF comprising introducing human cells into a human, wherein the human cells have been treated *in vitro* to insert a DNA segment encoding the cytokine other than TNF; and 2) a process for providing a human with a therapeutically effective amount of a therapeutic protein comprising introducing human B-lymphocytes into a human, wherein said human B-lymphocytes have been treated *in vitro* to insert a DNA segment encoding the therapeutic protein. Regarding 1), the process as claimed broadly reads on the introduction of any type of transfected human cell which expresses a cytokine other than TNF. The specification in column 5, lines 20-24, discloses the following cytokines: interleukins 1-12, and the alpha, beta, and gamma interferons. In terms of human cells for use in the process, the specification discloses the use of blood cells or tumor cells, see column 2, lines 46-63, and other primary cells, see column 18, lines 12-18. Regarding 2) the process as claimed broadly reads on introduction of transfected human B-lymphocytes which express any therapeutic protein. The specification discloses a number of candidate proteins, and further teaches that these processes are to be used for treating diseases such as cancer, emphysema, ADA deficiency, sickle cell anemia, thalassemia,

hemophilia, diabetes, Alzheimer's disease, growth disorders, and heart disease. In terms of inserting the DNA segment encoding the therapeutic protein into the cells, the specification generally states that any gene transfer methods can be used, and in particular retroviral transduction. It is further noted that the claims as written read on the transplantation of allogeneic human cells.

The specification does not provide an enabling disclosure for the therapeutic expression of any protein, including any cytokine, by administering any type of human cell, whether B-lymphocytes or other types of primary cells, to a human. While the specification provides a broad general description on the cells to be transfected, therapeutic genes to be expressed, and diseases to be treated, the majority of the specification is specifically directed to the treatment of either ADA deficiency or cancer by administering autologous human T lymphocytes obtained from peripheral blood or autologous human tumor-infiltrating lymphocytes (TIL), primarily composed of T lymphocytes, which have been transfected *ex vivo* with recombinant retroviruses which encode and express either ADA or TNF respectively. The working examples also disclose protocols for treating cancer by administering autologous tumor cells transduced *ex vivo* with recombinant retroviruses encoding TNF or IL-2, followed by the administration of TIL and recombinant IL-2 protein. Although the working examples describe protocols for preparing transduced autologous human TIL or tumor cells, the specification only provides actual data for human peripheral blood T-lymphocytes transduced with retrovirus encoding ADA. Working example 5 provides data for the treatment of a single patient with transduced autologous T-lymphocytes expressing ADA. Figures 4 and 5 demonstrate that following multiple infusions of transduced T -lymphocytes, in dosages varying from 0.6X10-9 cells to 18X10-9 cells, the patient

had detectable levels of transduced T cells in the blood secreting detectable levels of ADA. However, it is noted that the specification does not indicate whether the level of ADA expression observed correlated with any particular therapeutic effect on the patient. In regards to the other protocols set forth in the specification, the examples do not provide any specific guidance on the dosages of TIL or tumor cells expressing any particular level of TNF or IL-2 which correlates with a therapeutic effect on any type of cancer. It is further noted that the specification fails to provide any guidance for using allogeneic human cells. In addition, the specification fails to provide any specific guidance for transducing B lymphocytes, or provide any guidance or evidence regarding the treatment of any disease by administering transduced B lymphocytes expressing a therapeutic protein.

At the time of filing, circa 1991, the field of gene therapy was in its infancy. The skilled artisan at the time of filing did not consider the therapeutic transplantation of transfected/ transduced human cells into human patients as either routine or predictable. In 1987, the Los Angeles Times reported that most researchers skilled in the field of gene therapy believed that successful gene therapy in humans was still years in the future (Barry Siegel, Los Angeles Times, Sunday edition, December 13, 1987, "GENES: Debate over Human Experimentation: Part I"). In the same article, Richard Mulligan stated that as of 1987, "[t]here is absolutely no shred of evidence that it will work" (ibid, page 37). Stuart Orkin agreed stating, "[g]ene therapy is a stunt...[w]e are just plodding along right now. We don't know why or what works" (Los Angeles Times, Monday edition, December 14, 1987, "GENES: Debate over Human Experimentation: Part II"). In 1989, Buderi reported that on progress in gene therapy, "..scientists discovered that gene therapy isn't so simple after all. Even finding a means of

inserting a gene into a person-most approaches use a stripped-down retrovirus to deliver the new gene-has proven to be a quagmire of unforeseen problems. And if they solve these problems, scientists face the monumental task of inducing the inserted gene to produce the right amount of enzyme (or other protein missing in each genetic disease) at the right time" (Robert Buderi, The Scientist, 1989, Vol. 3, No. 2, pages 1-3, see page 2). Summing up the opinions of the skilled researcher in 1989, Boderi stated, "[t]hese researchers have learned from hard experience that the underlying science necessary for successful gene therapy is still in its infancy" (ibid, page 3). Friedmann, also reviewing the progress of human gene therapy in 1989, found that many problems remain to be solved before successful human clinical application could be expected, including problems with the efficiency of gene delivery and expression, problems with stable expression, and problems identifying, culturing, genetically modifying, and transplanting appropriate cell types to treat different diseases (Friedmann, Science, June 16, 1989, Vol. 244, Issue 4910, page 1275-1281). Regarding the use of retroviruses to transfer and express genes in cells, Friedmann states that integrated retroviral sequences show high-frequency structural and functional instability, and that, "..vector design, the nature of the target cell, the presence or absence of selection pressure, and the nature of the expressed genes can contribute to vector instability by mechanisms still not fully understood" (Friedmann, page 1276). Friedmann also specifically teaches that the expression of retrovirally transduced genes in bone marrow cells and other less differentiated cells is transient and unstable (Friedmann, page 1278). In addition, Friedmann identifies specific problems with identifying and genetically modifying appropriate cells for particular genetic diseases. Regarding genetic diseases of the CNS, Friedmann states, "[e]xperience with [Lesch-Nyhan disease] and others such as Alzheimer's and Parkinson's

disease has made it clear that genetic approaches to the dysfunctioning mammalian CNS are not entirely straightforward. Useful models for genetic approaches to therapy of CNS disorders are difficult to identify for the following reason: (i) little is known about normal or abnormal CNS function, (ii) the organ and many of its cells are inaccessible both physically and physiologically, and (iii) most disorders affecting CNS function are likely to be multigenic and multifactorial. Furthermore, most of the presumed target cells for CNS disorders, neurons, are postmitotic and therefore refractory to infection with retroviral vectors" (Friedmann, page 1278). In 1990, Culliton reported on the approval process for two gene therapy protocols in humans, and in particular one for treating malignant melanoma by administering autologous TIL retrovirally transduced to express TNF. Culliton quotes Rosenberg, one of the instant inventors, as saying that, "So far, gene therapy has been an abstract idea, and it is easy to think about the risks when there are no evident benefits. The climate will change if the experiments work." (Culliton, Science, August 31, 1990, Vol. 249, Issue 4972, pages 974-976, see page 976). Further, in 1992, reviewing progress in human gene therapy, Roemer and Friedmann conclude that while progress has been made toward the genetic correction of disease, " ..the permanent correction of a phenotype based on a genetic defect in humans by means of gene transfer and expression has so far not been achieved" (Roemer and Friedmann, Eur. J. Biochem., 1992, Vol. 208, 211-225, see page 223). Roemer and Friedmann also state in regards to human clinical trials underway as of 1992, that, "[t]hese and other experiments will certainly provide information in the near future about whether our current technical skills are sufficient to permit long-term correction of genetic disorders in human patients. Whatever the conclusion of these studies may be, we are optimistic that further progress in manipulating the human genome will eventually lead to means of

overcoming many human maladies" (ibid, page 223). Thus, it is clear that up to the time of filing in December of 1991, the skilled artisan did not consider gene therapy of humans as predictable. Furthermore, even after the time of filing, the unpredictability of human gene therapy continued to be recognized by the skilled artisan. In 1993, Mulligan reviewed the basic technical hurdles to successful gene therapy in humans and concluded that, "[t]he transplantation of transduced cells remains the most serious technical obstacle to the successful development of ex vivo gene therapies.", and that, " [t]he major technical limitation of current methods for delivering genes in vivo is that the persistence of the transferred genes is transient, and therefore gene expression is transient as well" (Mulligan, Science, May 14 1993, Vol. 260, Issue 5110, pages 926-932, see page 931). Mulligan also states that, " ..basic science issues underlie many of the problems that need to be overcome in order for gene therapy to succeed" (ibid, page 931).

From the above discussion of the state of the art of gene therapy, it is clear that several key problems with *ex vivo* human gene therapy were well known to the skilled artisan at the time of filing. In particular, the art cited above identified problems with the instability of the commonly used retroviral vectors in cells, difficulties in successfully transducing less differentiated and non-dividing cells, problems with transient gene expression, and problems associated with the persistence of the transduced cells once they are transplanted into the host. The specification fails to provide sufficient guidance to overcome these significant problems such that the skilled artisan would predict success in expressing therapeutic levels of a protein following the disclosed methods of *ex vivo* gene therapy. Regarding the ability to successfully transduce various cell types, while the specification broadly discloses the transduction of any primary human cell, including bone marrow stem cells, the specification only provides specific

guidance for transducing human T lymphocytes present in peripheral blood or TIL. It is noted that while the specification proposes a protocol to transduce human tumor cells, no actual data is provided. In view of the physiological differences between cells types, and the teachings in the prior art that many cell types and particularly bone marrow and non-dividing cells are refractory to retroviral transduction, see above, the skilled artisan would not be able to extrapolate the applicant's results with T lymphocytes to other types of cells including tumor cells, bone marrow cells, or B lymphocytes. Further, as discussed above, while the applicant's working examples do demonstrate that multiple infusions of retrovirally transduced T -lymphocytes expressing ADA, in dosages varying from 0.6X10-9 cells to 18X10-9 cells, resulted in detectable levels of transduced T cells in the blood secreting detectable levels of ADA, there is indication that this level of transduced T cells expressing this amount of ADA is in fact a therapeutic amount, or is capable of successfully treating ADA deficiency. In addition, there is no evidence presented in the specification that other types of cells transduced with the same retrovirus encoding ADA would be capable of persisting in the human host and expressing the same level of ADA as the transduced T lymphocytes. In regards to the expression of other genes, and particularly cytokines other than TNF, such as interleukins or interferons, the specification provides no specific guidance as to the level of expression of any of these proteins which correlates with a therapeutic effect on any disease or condition, or provide any evidence that any type of human cell transduced with the disclosed retroviral vectors, or any other type of vector, would be capable of stably expressing such a therapeutic level of each protein once transplanted into a human host.

In addition, the specification and working examples are all directed to the use of autologous human cells. However, as noted above, the claims as written broadly read on the use

of either allogeneic or autologous human cells. At the time of filing, the problems associated with the transplantation of allogeneic tissue were well known. Selden et al., for instance, teaches that the survival of transduced cells and the expression of recombinant proteins from the transduced cells in the host is significantly reduced if the cells are allogeneic, due to immune responses against the foreign antigens present on the allogeneic cells (Selden et al. Science, May 8, 1987, Vol. 236, pages 714-718, see page 717). The specification provides no guidance concerning the transplantation of allogeneic human cells to overcome the problem of immune rejection.

Therefore, in view of the undeveloped state of the art of human gene therapy at the time of filing, the recognition in the prior art of the high level of unpredictability of successful human gene therapy, the art recognized problems associated with achieving the expression of therapeutic levels of protein expressed from transduced cells *in vivo*, the lack of guidance provided by the specification for overcoming the art recognized problems, the lack of correlation between applicant's single working example which demonstrates detectable expression of a single gene from transduced autologous T lymphocytes and the therapeutic expression of any type of therapeutic protein including interleukins and interferons from any type of transduced human cell, including B lymphocytes, and the breadth of the claims, it would have required undue experimentation for the skilled artisan to practice the processes for providing a human with a therapeutically effective amount of a therapeutic protein as claimed.

No claims are allowed.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., whose telephone number is (571) 272-0737. The examiner can be reached Monday- Friday from 9:30-6:00 EST. If the examiner is not available, the examiner's supervisor, Ram Shukla, can be reached at (571) 272-0735. For all official communications, **the new technology center fax number is (571) 273-8300**. For informal, non-official communications only, the examiner's direct fax number is (571) 273-0737.

Dr. A.M.S. Wehbé

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER